

Emergence of YMDD Mutant Hepatitis B Virus after Allogeneic Stem cell Transplantation from a HBsAg-Positive Donor during Lamivudine Prophylaxis

There is no published report of emergence of a YMDD mutant in a HBsAg-negative patient who, under lamivudine prophylaxis, underwent allogeneic stem cell transplantation from a HBsAg-positive donor. To our knowledge, this is the first case of YMDD mutant developing from donor HBV.

Haematologica 2004; 89(3):e30-e31

A high incidence of HBV-related hepatitis is associated with the use of HBsAg-positive marrow for transplantation, and the high viral load in the donor appears to predispose recipients to the development of HBV-related hepatitis postransplant.¹ Preemptive use of lamivudine has proved to reduce hepatitis B exacerbation in HBsAg-positive recipients of allogeneic HCT.² Since 2000, the policy in our medical center has been to use lamivudine prophylaxis in HBsAg-positive patients or recipients with a HBsAg-positive donor. We report a case of the emergence of YMDD mutant in an anti-HBs-positive patient with T-cell lymphoblastic lymphoma receiving allogeneic hematopoietic stem cell transplant from a HBsAg-positive donor.

A 37-year-old man with relapsed lymphoblastic lymphoma received allogeneic bone marrow transplantation (BMT) from a matched unrelated donor. The conditioning regimen consisted of cyclophosphamide, total body irradiation and antithymocyte globulin. Before BMT, a serological examination showed that the donor had normal liver function and was HBsAg-positive, HBeAg-negative, anti-HBe-negative, and without detectable HBV DNA. The patient was anti-HBs-weak positive (82.1 mIU/mL), HBsAg-negative, anti-HBc IgG-negative. Lamivudine 100 mg /day was given to the recipient to inhibit replication of HBV one week before BMT. Engraftment with an absolute neutrophil count >500/ μ L was noted on D14. Herpes simplex virus type I was identified and persisted in his oropharynx from D14. Because cytomegalovirus (CMV) reactivation occurred on D23, the patient was given 14 days of preemptive ganciclovir therapy. Bilirubin increased progressively with moderate elevated ALT, ALP, and normal prothrombin time (PT) from D27 (Figure 1). The patient developed a fever at the same time. An abdominal echo revealed no biliary obstruction. Examination of HBV markers at that time revealed that the patient was still HBsAg negative, anti-HBs-positive, anti-HBc IgM-negative, but that his HBV DNA had risen to 3.4×10^7 copies/mL; a second analysis 2 weeks later yielded 1.3×10^8 copies/mL. Because his PT was normal throughout the whole course, intrahepatic cholestasis was suspected. The probable cause of his intrahepatic cholestasis included acute hepatitis B, acute GVHD, other virus infection, sepsis, or drug toxicity, and hepatitis activation was strongly suspected. A liver biopsy was not done for his thrombocytopenia. Graft rejection began on D35, and the patient died of multi-organ failure and intracranial hemorrhage on D49. HBV DNA from serum was amplified by polymerase chain reaction for direct sequencing of the DNA polymerase region. The YMDD mutant (M552I) was present.

The lamivudine-resistant HBV viruses have a characteristic amino acid substitution over tyrosine-methionine-aspartate-aspartate (YMDD)-motif of the RNA-dependent DNA polymerase. The methionine at codon 552 is

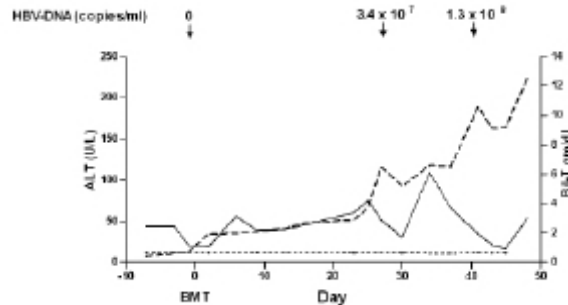


Figure 1. Clinical course and main laboratory data of the patient. BMT: bone marrow transplantation, ALT: , Bil: , PT: .

replaced by either an isoleucine (M552I) or a valine (M552V). YMDD mutants often emerge after prolonged lamivudine therapy. Hepatitis B virus with YMDD mutations is replication defective. *In vitro* studies have shown that this mutation reduced the effect of lamivudine on HBV replication by at least 20- to 100-fold.³ The reported incidence of YMDD mutations after one and two years of lamivudine therapy is 15% and 38%, respectively.⁴ In immunocompetent patients with chronic hepatitis B, YMDD mutants have seldom been detected before 36 weeks of lamivudine therapy.⁵ In liver transplant recipients with hepatitis B, resistance develops more rapidly in up to 30% of patients within as little as 6 months of continuous therapy.⁶ In our patient, however, the mutation occurred within one month post-transplantation. YMDD mutants have been detected in both untreated chronic hepatitis B patients and asymptomatic HBV carriers.^{7, 8} We do not know whether the mutant form already existed or was induced by the lamivudine therapy. Unfortunately, this question cannot be answered, because HBV DNA was undetectable in the donor.

The selection of lamivudine-resistant mutants is usually associated with a benign clinical outcome with transaminases and HBV DNA levels remaining below pre-treatment levels.⁵ In contrast to the commonly benign course of hepatitis after resistance to lamivudine emerges in chronic hepatitis B, however, the selection of lamivudine-resistant HBV in liver transplant recipients has been accompanied by sudden onset of liver failure and high levels of HBV replication after transplantation.³ A YMDD mutant did develop in one of 20 HBsAg-positive patients who had received lamivudine one week before allogeneic HC,² but never developed from donor HBV. New nucleoside analog such as adefovir and entecavir have proved effective against HBV YMDD mutants.^{9, 10} The effects of these agents in HBV-positive patients receiving stem cell transplantation warrant further study.

In conclusion, we advocate testing for the lamivudine-resistant YMDD mutant in any susceptible recipient after transplantation regardless of the presence of HBV antigenemia under lamivudine prophylaxis.

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Key words: Stem cell transplantation, Hepatitis B, YMDD mutation, Lamivudine

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